

## Original article

**Effect of ultrasound-detected synovitis on therapeutic efficacy of hyaluronic acid injection for symptomatic knee osteoarthritis**Chien-Chih Wang<sup>1,2</sup>, Chin-Tien Wang<sup>2</sup>, Kun-Ling Tsai<sup>3,4</sup>, Chen-Liang Chou<sup>5,6</sup>, Jian-Kang Chao<sup>7,8</sup>, Hsin-Yi Huang<sup>2,9</sup> and Chung-Lan Kao<sup>2,5,6,10</sup>**Abstract****Objective.** To determine whether ultrasound (US)-detected synovitis affects the therapeutic efficacy of hyaluronic acid (HA) injection for treating knee OA.**Methods.** Patients with symptomatic knee OA were recruited. All the patients received HA injection two times at 2-week intervals. Clinical assessments were performed using a visual analogue scale (VAS) and the Western Ontario and McMaster Universities OA Index (WOMAC) at baseline and 1 and 6 months after treatment. Imaging evaluation was based on complete knee US examination and the Kellgren–Lawrence grading. Suprapatellar synovial fluid (SF) depth, synovial hypertrophy (SH) and vascularity were measured through US.**Results.** In total, 137 patients who fulfilled the inclusion criteria were included in the analysis. All patients demonstrated improvement in VAS and WOMAC scores at 1 and 6 months after treatment ( $P < 0.001$ ). Moreover, regression model-based analysis revealed significant associations of SF depth with the VAS and WOMAC scores in all patients. Each centimetre increase in the effusion diameter was associated with a decrease in the 1-month post-treatment VAS improvement percentage (15.26; 95% CI: 0.05, 29.5;  $P = 0.042$ ) and 6-month post-treatment WOMAC improvement (37.43; 95% CI: 37.68, 50.69;  $P < 0.01$ ). However, SH and vascularity were not significantly associated with VAS or WOMAC scores.**Conclusion.** Ultrasound detected suprapatellar effusion predicts reduced efficacy of HA injection in knee OA**Key words:** ultrasound, osteoarthritis, knee pain, synovitis, hyaluronic acid**Rheumatology key messages**

- Ultrasound-detected synovial fluid depth in knee OA is significantly associated with HA injection outcome.
- Synovial hypertrophy and synovial vascularity did not affect the HA injection outcome.
- The synovial fluid depth must be used cautiously in combination with KL grade for more accurate prediction.

**Introduction**

Knee OA (OA) is one of the most prevalent conditions contributing to functional disabilities and pain [1]. Progressive low-grade inflammation, rather than degeneration, in the knee might play the main pathological

role in knee OA [2]. In the knee, synovium is the most critical source of nutrients for the chondrocytes within the cartilage and plays a role in maintaining the homeostasis of peri-joint soft tissues, which become inflamed and swollen in response to the initial trigger of injury or inflammation [3]. This inflammation, termed synovitis, causes excess fluid secretion into the knee bursa, synovial hypertrophy (SH) and increased vascularity. Knee

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synovitis stimulates the peripheral nerve, which contributes to severe pain in the initial Kellgren–Lawrence (KL) stages [4]. An increase in the amount of the synovial fluid (SF) also causes knee stiffness during ambulation. Knee effusion and associated synovitis are strongly correlated with the clinical symptoms of knee OA and structural damage [5].

Musculoskeletal ultrasound (US) is a widely used tool for detecting soft tissue injury and inflammation [6]. However, its diagnostic sensitivity and specificity are not superior to those of MRI. Nevertheless, in contrast to X-ray imaging, US facilitates real-time imaging of peripheral vascularity, perisynovial oedema and cartilage erosion for early detection of synovitis. US is considered the gold standard for the detection of rheumatological synovitis. In our previous US-based study, hyaluronic acid (HA) injection was confirmed to reduce hyperaemia and alleviate clinical symptoms in an ankle affected by rheumatoid arthritis, further emphasizing the effectiveness of US as a prognostic tool for evaluation of the synovial condition [7]. US also serves as an efficient tool for synovitis outcome measurement in knee OA [8]. The clinical symptoms of effusion-related synovitis and those of Hoffa's fat pad synovitis are closely related [5]. US has synovitis detection sensitivity comparable to MRI—the diagnostic gold standard for knee pathology—and thus remains the most useful tool for detecting synovial inflammation of the knee [9–11].

Although US-detected synovitis has been confirmed to be partially correlated with initial pain-related symptoms in knee OA, no study has focused on the use of US for predicting the efficacy of intraarticular injection of drugs such as HA. HA injection is an alternative intraarticular OA treatment strategy, with main therapeutic effects being lubrication, inflammation and pain reduction, and potential tissue repair [12]. Several studies have favoured the clinical efficacy of HA injection for OA. However, results have been heterogeneous—with some studies reporting borderline efficacy and others demonstrating efficacy similar to normal saline injection [13, 14]. Several current treatment guidelines for knee OA also do not include HA injection as a recommended therapy due to inconsistent conclusions [15–18]. Despite the consensus that advanced knee OA (based on KL grading) responds poorly to HA injection, whether synovitis affects the therapeutic efficacy of HA injection in knee OA treatment remains unclear. In this present study, we hypothesized that US-detected knee synovitis influences the therapeutic outcomes of HA injection in knee OA. Both KL grade and synovitis may contribute to this association.

## Methods

We conducted a prospective cohort study. In total, 143 patients with symptomatic knee pain visiting the Physical Medicine and Rehabilitation outpatient clinic at the Yuli branch of Taipei Veterans General Hospital were enrolled. The study was conducted from 2016 to 2019.

The study protocol was approved by the Ethics Committee of Taipei Veterans General Hospital, and all patients provided written informed consent. Inclusion criteria were the following: (i) clinical and radiographic diagnosis of knee OA met ACR criteria [19, 20], (ii) age >40 years, (iii) disease duration  $\geq 1$  month, (iv) no knee deformity or ankylosis, and (v) no active disease flareup or other substantial infections or inflammatory disease. Patients were excluded if their treatment required immediate adjustment and if they had severe active diseases, such as infections or inflammatory diseases, previous steroid injection within 3 months or a history of allergy to HA injection.

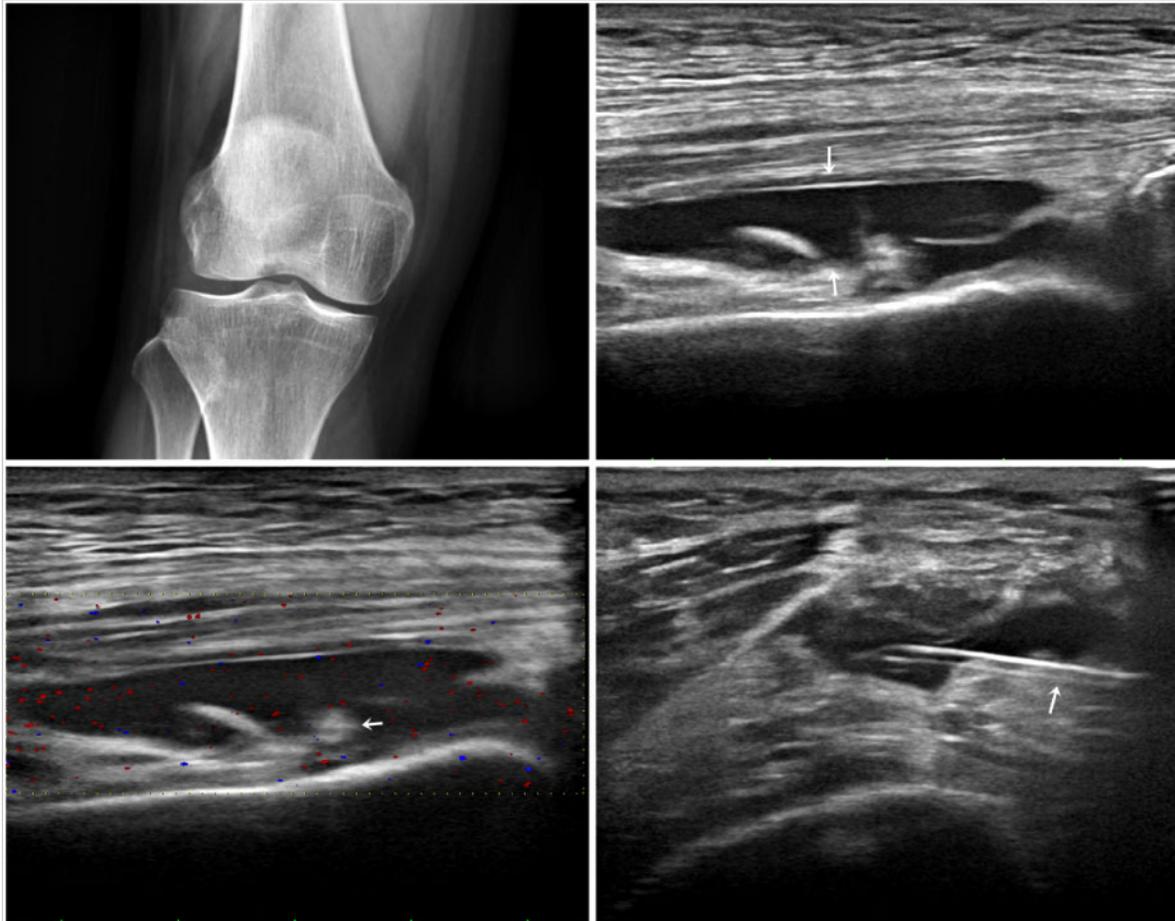
All the patients received the low-molecular-weight HA (Hyalgan R, 500–730 kDa HA, Bioibérica SA, Barcelona, Spain; molecular weight:  $0.5 \times 10^6$ ) injection twice at 2-week intervals of hospital visits, which included baseline evaluation with subsequent first HA injection and 2 weeks later with the second HA injection.

Detailed physical examination and history taking were performed before HA injection. If the baseline US examination revealed effusion over the suprapatellar bursa, complete drainage was performed to prevent the dilution of HA. After drainage, 2.5 ml of HA was injected into the suprapatellar bursa under US guidance. Moreover, all the patients were told not to receive other interventions such as exercise or life style modification. Oral or topical analgesics were also not encouraged over the course of the evaluation period.

## Outcome measures

Clinical outcomes were measured at baseline before injection and at 1 and 6 months after completion of the 2-week injection course through face-to-face visits. We assessed global pain by asking the patients to self-report their daily average pain levels by using a 100-mm visual analogue scale (VAS). Knee function and pain were assessed using the Western Ontario and McMaster Universities OA Index (WOMAC), a validated self-administered questionnaire for measuring OA-related knee pain and disability [21], comprising three subscales: functional knee pain (WOMAC<sub>pain</sub>, five items), stiffness (WOMAC<sub>stiff</sub>, two items) and physical function (WOMAC<sub>phy</sub>, 17 items), all scored on a 0–4 scale. The sum of the three subscale scores provides a total WOMAC score (WOMAC<sub>total</sub>) ranging from 0 to 100. We recorded the following demographic and clinical characteristics at baseline: age; sex; duration of knee pain; body mass index ( $\text{kg}/\text{m}^2$ ); and history of hypertension, hyperuricaemia or hyperglycaemia. Radiographic severity was evaluated through anteroposterior knee X-ray examination in the standing position and graded on the KL scale [22].

Examinations were performed in accordance with the recommendations of the European League Against Rheumatism by using a Hitachi Aloka Ultrasound System (Prosound F75, Tokyo, Japan) equipped with a 6–18-Hz linear transducer [11]. Grey-scale imaging and power Doppler (PD) techniques were used to examine

**Fig. 1** Osteoarthritic synovitis revealed through US and a guided procedure

**(A)** Case with KL grade II OA. **(B)** Suprapatellar effusion was investigated with US, and the depth (between the two white arrows) was measured for a 30° knee flexion. **(C)** The PD flow revealed grade 0–1 vascularity. The SH (indicated by the arrow) was measured. **(D)** US-guided aspiration of the fluid was conducted and then HA injection (white arrow points to the needle tip) was performed after baseline evaluation.

the knee, and the grey-scale US image was adjusted for maximal contrast and gain according to the level at which noise appeared. A full ultrasound examination of knee was performed. The suprapatella bursa rather than the medial or lateral recess was measured (Fig. 1).

Subsequently, a spectral Doppler US was used to confirm that the power flow signal represented the actual blood flow rather than an artefact. The interobserver and intraobserver reliability test results were reported previously [23]. The PD signals were evaluated using a semiquantitative technique [24] on a 0–3 scale, where 0 indicates no Doppler signal (colour pixel) or no flow, 1 indicates a single Doppler signal or low flow (either three single spots or two single spots and one confluent spot), 2 indicates several Doppler signals ( $\leq 50\%$  colour pixels of the intraarticular area), and 3 indicates a complete joint area with coherent Doppler signals or strong flow ( $\geq 50\%$  colour pixels of the intra-articular area). SF depth in the suprapatellar bursa was measured with the knee bent at 30°. The highest possible vertical line that

could be drawn from the top of the bursa was measured (in cm). Maximal SH was also measured.

#### Data analysis

Statistical analysis and data evaluation were performed using SPSS (version 12.0; SPSS Inc., Chicago, IL, USA). At baseline, an independent Student's *t*-test was used to assess continuous data, and the  $\chi^2$  test was conducted to assess categorical data. The level of significance was set at  $P < 0.05$ . The percentage score improvement was calculated [(post-evaluation scores – baseline scores)/baseline scores] to perform a between-group comparison. The score improvement percentages for WOMAC and VAS scores were calculated and analysed using analysis of covariance. The baseline WOMAC and VAS data exhibited covariance. Ordinal data such as PD-US values and laboratory data were analysed using the non-parametric Mann–Whitney *U* and Kruskal–Wallis tests.

A multiple regression test was used to clearly elucidate the role of synovial inflammation in HA injection efficacy. The method was similar to the previous study using regression analysis to find the association between baseline clinical VAS and imaging modality of US and KL grade [5]. The dependent variable was VAS/WOMAC percentage change and the independent variable was SF depth and KL grade. Associations between >50% improvement and imaging were identified through logistic regression.

## Results

### Patient demographics and characteristics at baseline and change of clinical presentation scores before HA injection

Of the 143 recruited patients, six could not complete the evaluation for personal reasons, and so 137 patients completed the experimental protocol.

The majority of patients (60.6%) were male, which was different from a previous report that women were more susceptible to OA and may be specific to our study [25]. The low grade inflammation ultrasound assessment revealed that the mean grade of PD signal was 1.5. The mean synovial effusion depth was 0.53 (0.47–0.57) cm in diameter. Two cases presenting with SF depth >1 cm in diameter were found to have high KL grade (grade 3 and 4 each) (Table 1). SF depth was significantly but weakly associated with the baseline clinical symptoms of VAS ( $R = 0.267$ ,  $P < 0.01$ ) and WOMAC ( $R = 0.298$ ,  $P < 0.01$ ).

### Association between synovial fluid depth, VAS and WOMAC without adjustment of KL grade

All patients demonstrated reduced mean VAS and WOMAC scores at both 1 and 6 months after treatment (both  $P < 0.001$ ; Table 2).

The association between SF depth and change in VAS scores (i.e. improvement) was significant at

**TABLE 1** Baseline characteristics of the study population

Characteristic	Value ( $n = 137$ )
Age, mean (95% CI), years	67.5 (65.3, 69.6)
Female gender, $n$ (%)	57 (39.4)
BMI, mean (95% CI), kg/m <sup>2</sup>	25.1 (22.9, 27.2)
OA stage, median (IQR)	3 (2–4)
Disease duration, mean (95% CI), months	22.22 (11.12, 33)
Global pain, mean (95% CI), VAS score	54.6 (51.3, 60.0)
WOMAC score, mean (95% CI)	57.2 (53.7, 60.6)
Effusion depth, mean (95% CI), cm	0.53 (0.47, 0.57)
Synovial hypertrophy, mean (95% CI), cm	0.38 (0.32, 0.43)
Power Doppler signal, mean (95% CI)	1.5 (1, 2)

IQR: interquartile range.

6 months after treatment ( $R = -0.216$ ,  $P = 0.024$ ) but not at 1 month after treatment ( $R = 0.091$ ,  $P = 0.343$ ). Moreover, the change in WOMAC scores and SF depth exhibited significant associations at 1 ( $R = -0.233$ ,  $P = 0.014$ ) and 6 ( $R = -0.471$ ,  $P < 0.01$ ) months after treatment (Fig. 2).

### Association between synovial fluid depth, VAS and WOMAC with adjustment of KL grade

Adjustment of KL grade through multiple linear regression was then performed to determine whether the association of SF depth with VAS and WOMAC change was still present at 1 and 6 months after treatment (Tables 3 and 4).

At 1 month after treatment, the association between SF depth and VAS change revealed no significance ( $P = 0.19$ ). The WOMAC percentage change was significantly associated with SF depth ( $P = 0.023$ ), with an effect size of  $-15.16$ , meaning that each additional increase of 1 cm of effusion depth contributed to 15.16% less WOMAC improvement. At 6 months after treatment, VAS change was significantly associated with SF depth ( $P = 0.042$ ), with an effect size of  $-15.26$ . This means that each additional increase of 1 cm of effusion depth contributed 15.26% less VAS reduction after treatment. The WOMAC percentage change also revealed a significant association ( $P < 0.01$ ), with an effect size of  $-37.43$ , meaning that each additional increase of 1 cm of effusion depth contributed to 37.43% less WOMAC improvement. KL grade was simultaneously revealed to be significantly associated with VAS improvement percentage at 1 and 6 months after treatment ( $P = 0.047$  and  $0.028$ , respectively), suggesting a KL grade effect on outcome improvement.

A response to the injection was defined as an improvement of >50% compared with the baseline evaluation. The response percentage in terms of WOMAC score improvement at the 6-month evaluation was significantly negatively associated with effusion (odds ratio = 0.024; 95% CI: 0.002, 0.298;  $P < 0.01$ ). By contrast, the 1-month VAS, 6-month VAS, and 1-month WOMAC evaluation results were not significant.

### Association between synovial hypertrophy and vascularity

The association between SH and clinical symptom improvement was non-significant for VAS improvement at 1 ( $P = 0.56$ ) and 6 ( $P = 0.43$ ) months after treatment, respectively, or for WOMAC improvement at 1 ( $P = 0.32$ ) and 6 ( $P = 0.12$ ) months after treatment, respectively. Moreover, the association between clinical symptom improvement and SH was non-significant, as indicated by PD-US values.

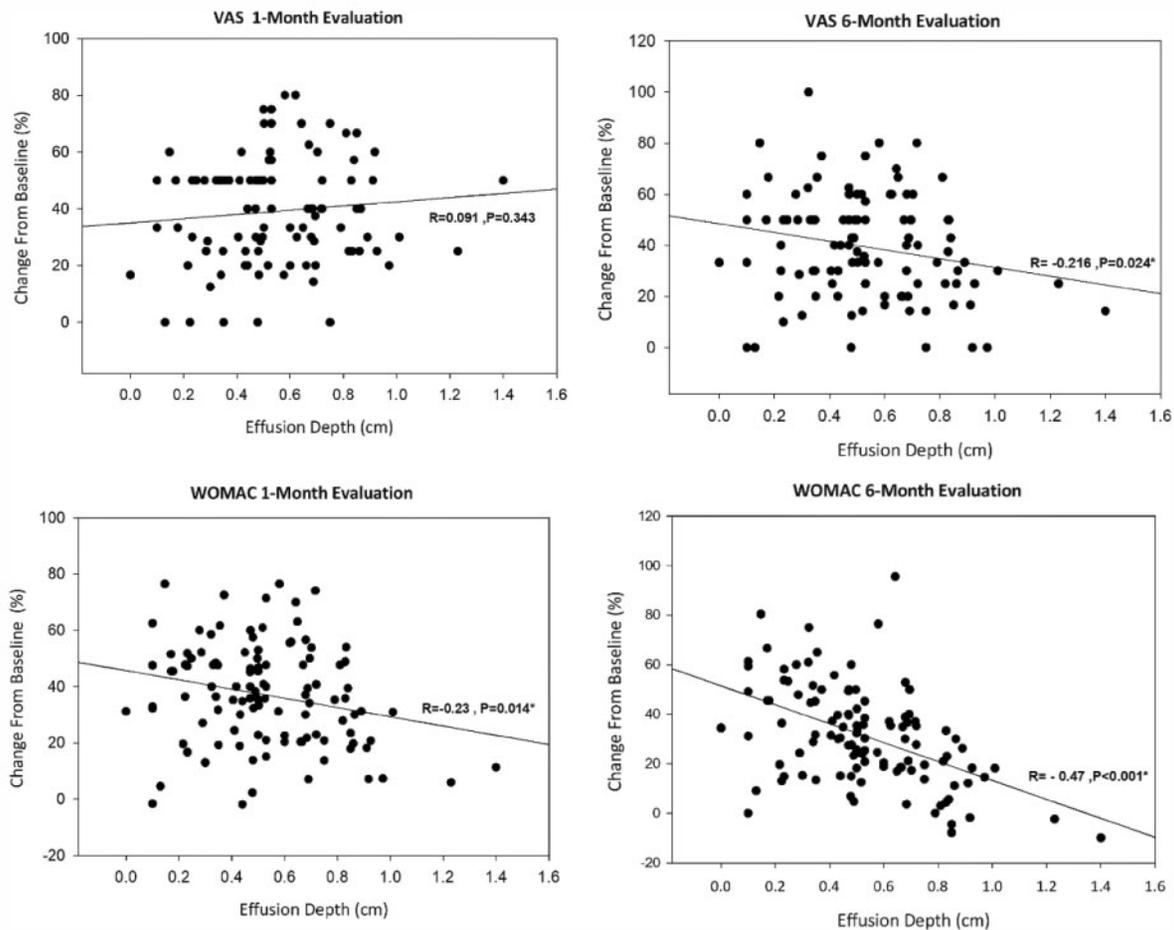
## Discussion

The current results demonstrate significant associations between both synovitis and the KL grade with clinical

**TABLE 2** VAS and WOMAC scores at 1 and 6 months after treatment

Outcome	Baseline	1-month evaluation	6-month evaluation	P-value (1 month to baseline)	P-value (6 months to baseline)
VAS	54.6 (51.3, 60.0)	33.2 (30.2, 35.7)	30.7 (27.6, 34.7)	<0.001 (1.91, 2.37)	<0.001 (1.76, 2.21)
WOMAC	57.2 (53.7, 60.6)	36.6 (33.4, 39.8)	39.8 (36.3, 43.3)	<0.001 (17.1, 21.3)	<0.001 (13.8, 18.3)

The values are presented as means (95% CI). VAS: visual analogue scale; WOMAC: Western Ontario and McMaster Universities Arthritis Index.

**Fig. 2** Spearman Rank Correlation for clinical symptom improvement (A) and effusion (B) to elucidate the negative association between them

\*Significant at  $p < 0.05$ .

outcomes of HA injection. The regression model used to predict pain and knee function according to SF depth indicates that the increased accumulation of SF is a crucial factor for determining the therapeutic efficacy of HA injection. Moreover, the long-term outcome measurement afforded more significant results than the short-term measurement, indicating that increased effusion is associated with symptom recurrence. US-detected SF fluid but not other synovial marker seems

to play an essential role in predicting the efficacy of HA injection in knee OA treatment.

Knee OA-related pain, a complex multifactorial condition, is mainly classified into structural abnormality and neurological disability [26]. Bone structural abnormalities such as cartilage degradation, osteophyte formation and bone remodelling revealed through radiography are critical factors contributing to ambulatory pain and functional limitation. Therefore, HA

**TABLE 3** Association between VAS change with SF depth and KL grade at 1 and 6 months after treatment<sup>a</sup>

VAS (% change) <sup>b</sup>	Absolute effect <sup>c</sup>	95% CI	P-value
1 month after injection			
SF depth (cm)	9.078	-4.76, 22.81	0.19
KL grade	-3.235	-6.32, -0.39	0.047 <sup>d</sup>
6 months after injection			
SF depth (cm)	-15.26	-29.9, -0.56	0.042 <sup>d</sup>
KL grade	-3.84	-7.26, -0.434	0.028 <sup>d</sup>

<sup>a</sup>Age, sex and body mass index adjusted in the regression model. <sup>b</sup>Percentage clinical change compared with baseline. <sup>c</sup>Absolute effects from linear regression models: refers to the change in the associated outcome variable with each further 1 cm SF depth increased and 1 further KL grade increased. <sup>d</sup>Statistically significant intergroup difference. KL: Kellgren-Lawrence; VAS, visual analogue scale.

**TABLE 4** Association between WOMAC change with SF depth and KL grade at 1 and 6 months after treatment<sup>a</sup>

WOMAC (% change) <sup>b</sup>	Absolute effect <sup>c</sup>	95% CI	P-value
1 month after injection			
SF depth (cm)	-15.16	-28.2, -2.21	0.023 <sup>d</sup>
KL grade	-2.71	-5.72, 0.317	0.079
6 months after injection			
SF depth (cm)	-37.43	-50.67, -37.68	0.001 <sup>d</sup>
KL grade	-1.67	-4.76, 1.41	0.283

<sup>a</sup>Age, sex and body mass index adjusted in the regression model. <sup>b</sup>Percentage clinical change compared with baseline. <sup>c</sup>Absolute effects from linear regression models: refers to the change in the associated outcome variable with each further 1 cm SF depth increased and 1 further KL grade increased. <sup>d</sup>Statistically significant difference. KL: Kellgren-Lawrence; WOMAC: Western Ontario and McMaster Universities Arthritis Index.

injection therapy is considered a palliative treatment in advanced knee OA [27]. A recent study suggested that HA injection is a cost-effective treatment for advanced knee OA and can delay total knee replacement [28]. Our results demonstrate that, regardless of KL or synovitis grade, HA injection improves both WOMAC and VAS scores, with the therapeutic effect lasting up to 6 months.

The US results reveal that SF depth, rather than SH, is associated with an improvement in HA injection efficacy, which indicates that effusion size may predict the degree of clinical symptom improvement. Similar studies have noted that effusion-related synovitis, but not synovitis of the perisynovial tissue, contributes to progressive cartilage loss [29, 30]. In addition, studies have stated that effusion-related synovitis is a better surrogate marker for structural damage in knees affected by OA [31]. This result is also consistent with a study by Sarmanova *et al.* that proposed cutoff values for synovial abnormality (7.4 mm in men; 5.3 mm in women) for US-detected effusion in patients with knee pain and OA [32]. This supports our finding of a significant association between an increased amount of SF and clinical improvement. Our findings also concur with previous findings that US-detected effusion 1 month after steroid injection can predict injection efficacy for up to 1 year, suggesting

that effusion also plays a role in predicting injection efficiency [8].

The association of the KL grade and synovitis grade with knee pain has not been well established. A study revealed that synovitis may not be independently associated with clinical symptom improvement after adjustment for the KL grade [5]. Another study found that effusion can predict exacerbation of knee pain, but this finding remained non-significant after adjustment for the KL grade [23]. Whether KL grade or synovitis grade played a greater role is not fully demonstrated. By contrast, the reason that SF effusion was independently associated with pain after adjustment for KL grade is possibly attributable to the therapy used in the present study, where the primary effect of HA is in the synovial cells. Effusion size may indicate synovial dysfunction with oversecretion and poor absorption of SF. HA injection alters synovial function [3]. Notably, short-term VAS improvement was associated only with KL grade but not with SF, suggesting an immediate pain reduction.

Although the KL grade was significantly associated with both pain and function improvement, the effect size was larger for SF depth. This could be explained by the fact that increased SF may lead to increased dysfunction in synovial lining cells, which generally secrete minimal SF and supply nutrients to chondrocytes in the

cartilage. As injury triggers the inflammation cascade, the cells' metabolism is disrupted [3], potentially causing overstimulation and poor absorption and thereby increasing SF depth. With the increased synovial cell dysfunction (as reflected by the SF depth), HA may provide only short-term pain relief rather than altering synovial function. This finding warrants further investigation, even though OA studies have demonstrated that HA has antiapoptotic and antioxidant properties [33, 34].

The present study found no association between PD and the percentage improvement of clinical symptoms, and baseline average PD for synovitis revealed low-grade vascularity, indicating that PD detection may not be a surrogate marker for OA. This result is consistent with a previous finding that PD signals are not commonly detected in pain related to knee OA [23]. In contrast to rheumatoid arthritis synovitis, which is characterized by abundant neovascularization and pannus formation contributing to hypervascularization, OA-related synovitis appears to manifest less inflammation [4, 35]. In this study, four patients presenting with persistent severe pain exhibited high vascularity and low response to HA injection. Of these patients, one was diagnosed as having rheumatoid arthritis after a series of blood tests, whereas another was diagnosed as having gouty arthritis. One possible reason for the ineffectiveness of the HA injection in these two patients was the presence of active inflammatory components. However, the cause of HA injection failure in the other two patients remains unclear. Although the efficacy of PD in detecting OA synovitis is not well understood, its efficacy in determining acute inflammatory status is well established.

This study has several limitations. First, the study was designed to primarily determine the association of US characteristics with clinical symptom improvement, but not with the duration of HA efficacy. Although the evaluation period was not as long as 1 year, the efficacy of low-molecular-weight HA injection was determined to last for ~3–6 months. Second, the drainage of effusion before injection may have some therapeutic effect on our finding that baseline VAS and WOMAC are associated with SF depth. However, the effect of drainage or joint lavage has been suggested to be temporary, with effusion easily reaccumulating within weeks [36, 37]. Therefore, the effect of fluid drainage may derive mainly from better interaction between HA and synovium due to drainage rather than the drainage of fluid itself. This warrants a further randomized study for confirmation.

Third, MRI was not used; therefore, subchondral bone marrow lesions, cartilage lesions and obvious meniscus lesions could not be detected. However, these lesions are less correlated with clinical symptom improvement, and only effusion synovitis and Hoffa synovitis are considered relevant [38, 39]. Although US cannot yield comprehensive measurements, the suprapatellar bursa (the largest bursa) is connected to other bursae [40], suggesting that SF effusion is the most representative marker of bursal defects. The sensitivity and specificity of US

and MRI for outcome measurement require further comparison.

In conclusion, this study highlights the association between US-detected SF depth and clinical symptom improvement after HA injection. Because of its representation of synovial status, SF depth was indicative of long-term outcomes. Although SF depth is independently associated with outcome, it must be cautiously used in combination with KL grade for more accurate prediction. US-detected SF depth appears to be a feasible and potentially accurate marker for outcome measurement in OA; however, further trials on synovitis are warranted.

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**Disclosure statement:** The authors have no competing interests to declare.

## Data availability statement

Data are available upon request from the corresponding author.

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